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Fifteen-year Outcomes Following Conservative Management Among Men Aged 65 Years or Older with Localized Prostate Cancer

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Abstract

Background—To understand the threat posed by localized prostate cancer and the potential impact of surgery or radiation, patients and healthcare providers require information on long-term outcomes following conservative management.

Objective—To describe 15-yr survival outcomes and cancer therapy utilization among men 65 years and older managed conservatively for newly diagnosed localized prostate cancer.

Design, settings, and participants—This is a population-based cohort study with participants living in predefined geographic areas covered by the Surveillance, Epidemiology, and

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End Results program. The study includes 31 137 Medicare patients aged ≥ 65 yr diagnosed with localized prostate cancer in 1992–2009 who initially received conservative management (no surgery, radiotherapy, cryotherapy, or androgen deprivation therapy [ADT]). All patients were followed until death or December 31, 2009 (for prostate cancer–specific mortality [PCSM]) and December 31, 2011 (for overall mortality).

Outcome measurements and statistical analysis—Competing-risk analyses were used to examine PCSM, overall mortality, and utilization of cancer therapies.

Results and limitations—The 15-yr risk of PCSM for men aged 65–74 yr diagnosed with screening-detected prostate cancer was 5.7% (95% confidence interval [CI] 3.7–8.0%) for T1c Gleason 5–7 and 22% (95% CI 16–35%) for Gleason 8–10 disease. After 15 yr of follow-up, 24% (95% CI 21–27%) of men aged 65–74 yr with screening-detected Gleason 5–7 cancer received ADT. The corresponding result for men with Gleason 8–10 cancer was 38% (95% CI 32–44%). The major study limitations are the lack of data for men aged < 65 yr and detailed clinical information associated with secondary cancer therapy.

Conclusions—The 15-yr outcomes following conservative management of newly diagnosed Gleason 5–7 prostate cancer among men aged ≥ 65 yr are excellent. Men with Gleason 8–10 disease managed conservatively face a significant risk of PCSM.

Patient summary—We examined the long-term survival outcomes for a large group of patients diagnosed with localized prostate cancer who did not have surgery, radiotherapy, cryotherapy, or androgen deprivation therapy in the first 6 mo after cancer diagnosis. We found that the 15-yr disease-specific survival is excellent for men diagnosed with Gleason 5–7 disease. The data support conservative management as a reasonable choice for elderly patients with low-grade localized prostate cancer.

Keywords

Prostatic neoplasm; Survival; Population-based study

1. Introduction

Prostate cancer is the most common non–skin cancer and the second most common cause of cancer death in the USA [1]. Because of widespread prostate-specific antigen (PSA) screening, most contemporary men are diagnosed with localized disease [2]. Treatment options for localized disease commonly include active surveillance or conservative management, surgery (radical prostatectomy), and radiation therapy.

A recent update of the Scandinavian Prostate Cancer Group 4 (SPCG-4) trial comparing surgery with watchful waiting reported a 12.7% absolute risk reduction in overall mortality for men aged < 65 yr undergoing surgery but no significant benefit for men aged ≥ 65 yr [3–5]. Similarly, the Prostate Intervention Versus Observation Trial (PIVOT) showed no improvement in disease-specific or overall survival for men with low-grade disease through 12 yr of follow-up [6]. More than half of the men in both trials were older than 65 yr at diagnosis. Unlike the situation for surgery, researchers have yet to publish large-scale

randomized comparisons of radiation therapy and active surveillance or conservative management.

Only a small percentage of men in the USA have their prostate cancer managed conservatively [7–9]. Furthermore, among men who initially choose conservative management, up to half switch to active treatment within 5 yr of diagnosis, and many do so without clinical evidence of disease progression [10]. Presumably, these men fear disease progression and are reluctant to forgo treatment.

To document the progression of low-grade prostate cancer, we previously reported 10-yr outcomes for a cohort of 14 516 men with localized T1/T2 prostate cancer diagnosed during 1992–2002 and managed conservatively [11]. Unfortunately, as documented in the watchful waiting arm of the SPCG-4 study, disease progression continues well beyond 10 yr [5]. We performed this study to provide long-term 15-yr follow-up data for men managed conservatively for newly diagnosed, localized prostate cancer.

2. Patients and methods

2.1. Data sources

Data were obtained from Medicare claims files linked to the population-based Surveillance, Epidemiology, and End Results (SEER) cancer registries, which are 98% complete for case ascertainment [12]. The SEER regions encompassed approximately 14% of the US population before 2000 and 25% thereafter [12]. The Medicare database covers approximately 97% of US individuals aged ≥ 65 yr. Linkage to the SEER database is complete for approximately 93% of the patients [12].

SEER data files provided information on cancer stage and grade for each case. Before 2003, Gleason 2–4, 5–7, and 8–10 cancers were grouped as well-, moderately, and poorly differentiated cancers, respectively. In 2003, Gleason 7 was grouped with Gleason 8–10 in SEER. In 2004, primary and secondary Gleason score information became available. In this study, we combined patients with Gleason 8–10 as poorly differentiated cancer except for 2003, for which Gleason 7 was included in the poorly differentiated group.

2.2. Study participants

The study cohort consisted of men aged ≥ 65 yr who were SEER residents and diagnosed with stage T1–T2 prostate cancer during 1992–2009 ($n = 382\,673$). Those who died or were censored within 180 d of cancer diagnosis or who had another cancer diagnosis were excluded ($n = 93\,020$) to ensure that all cancer therapies were for prostate cancer. Men who had surgery, radiation, or cryotherapy within 6 mo of diagnosis ($n = 171\,361$) or did not have both Medicare Part A and Part B as their primary health insurance coverage ($n = 47\,016$) during the study period were excluded. In addition, those with an unknown cancer grade or T1a/T1b cancer and those receiving androgen deprivation therapy (ADT) or palliative radiation therapy within 6 mo of diagnosis ($n = 40\,139$) were excluded. We excluded men with T1a/T1b cancers because they differ from contemporary patients with screening-detected cancer. We characterized the remaining 31 137 men as receiving conservative therapy.

2.3. Outcome assessment

Overall and prostate cancer-specific survival was available through December 31, 2011 and December 31, 2009, respectively. SEER data files provided information on the underlying cause of death. Previous studies have shown high agreement (87–92%) between the cause of death in the SEER database and that determined through medical record review [13, 14]. Detailed definitions of various cancer therapies have been described previously [11].

2.4. Statistical analyses

The primary study endpoints were time to death from prostate cancer and time to death from all causes, stratified by patient age, cancer grade, and stage at diagnosis. We estimated cumulative incidence accounting for the competing risks of death from other causes (Fig. 1, Tables 2 and 4) [15]. When analyzing the 15-yr risk of secondary cancer therapy, we computed the risk of each outcome independently because one individual could have had more than one secondary treatment. To provide smooth estimates of the survival curves, we used a nearest-neighbor hazard smoother with an Epanechnikov kernel [16] as implemented in the R statistical system (R Foundation for Statistical Computing, Vienna, Austria). We obtained 95% pointwise confidence bands for the smoothed hazard estimates using a bootstrap resampling procedure with 1000 bootstrap replications. The confidence bands at each time point reflect the upper and lower 2.5 percentile of the bootstrap replications at that point.

3. Results

Our study identified 31 137 men aged 65 yr diagnosed with localized prostate cancer during 1992–2009. The median age at diagnosis was 75 yr and the median follow-up time was 6.4 yr among survivors (3rd quartile, 9.5 yr). Table 1 summarizes the baseline characteristics of the study population. Most men (87%) had Gleason 5–7 tumors and 40% of men had PSA-detected disease (T1c).

There were 5257 patients alive in year 10 and 1138 patients in year 15. For men with Gleason 5–7 disease, the 15-yr prostate cancer-specific mortality (PCSM) was 5.7% for men aged 65–74 yr and 10% for men aged 75 yr (Table 2). For men with PSA-detected Gleason 8–10 disease, PCSM rates were much higher, at 22% and 27%, respectively.

Figure 1 shows a competing-risks analysis of death according to age at diagnosis, cancer stage, and grade. The numbers of men at risk at baseline and at 5, 10, and 15 yr in Figure 1 are shown in Supplementary Table 1. The 15-yr PCSM rates among men with Gleason 5–7 PSA-detected disease were lower for those aged 64–74 yr (5.7%; 95% CI 3.7–8.0%) than for those aged 75 yr (10.1%; 95% CI 8.1–12.4%; Table 2). The 15-yr PCSM rates among men with Gleason 8–10 disease were much higher, at 22% for men aged 65–74 yr and 27% for men aged 75 yr (Table 2). Analysis by comorbidity status (Supplementary Tables 2A–2C) shows that patients with a comorbidity score of 0 had mortality rates similar to the entire group, whereas patients with a higher comorbidity score had lower PCSM rates because of deaths from competing risks. To assess whether PCSM changed over time, comparisons of unadjusted PCSM rates according to follow-up period are summarized in Table 3. Overall, PCSM rates remained stable beyond 5 yr in our study. Table 4 summarizes the 15-yr

cumulative risk of receiving secondary cancer therapies. Among men with PSA-detected Gleason 5–7 cancer diagnosed before the age of 75 yr, 54% received attempted curative treatment within 15 yr of diagnosis. Of those who elected for treatment, approximately 80% underwent surgery or radiation within 2 yr of cancer diagnosis. Among men with Gleason 5–7 PSA-detected disease, 24% of those 65–74 yr and 33% of those aged ≥75 yr received ADT within 15 yr of diagnosis. Approximately 4.9% (95% CI 3.4–7.2%) of these men received chemotherapy. Among men with Gleason 8–10 PSA-detected cancer, 38% of those aged 65–74 yr and 45% of those aged ≥75 yr received ADT. Approximately 8.3% of men aged 65–74 yr and 5.4% of men aged ≥75 yr received chemotherapy. Analysis by comorbidity status shows that patients with no comorbidity are less likely to have ADT compared to patients with a comorbidity score of 1 among men aged 65–74 yr, but not among men aged ≥75 yr (Supplementary Tables 3A–3C). Procedures codes used to identify secondary treatments in Table 4 are listed in Supplementary Table 4.

4. Discussion

To evaluate the threat posed by newly diagnosed prostate cancer, men must have information on disease progression in the absence of treatment. PSA testing has identified large numbers of men with localized prostate cancer, but most contemporary information on the course of this disease was collected from men diagnosed in the pre-PSA era.

The current study estimates the 15-yr risk of dying from prostate cancer or other causes among men diagnosed with localized cancer in the PSA era. For men with Gleason 5–7 PSA-detected prostate cancer, the 15-yr risk of PCSM was < 10%, and approximately half of the men did not require cancer therapy within 15 yr of follow-up. These results are comparable to those reported by Wilt et al for the observation arm of the PIVOT trial [6] and by Bill-Axelson et al for the observation arm of the SPCG-4 trial [4, 5]. PCSM was 5% in the PIVOT trial after 12 yr [6] and 10% in the SPCG-4 trial after 15-yr follow-up [4]. Results in our contemporary PSA-era study cohort were considerably better than survival outcomes reported by Albertsen et al [17] and Johansson et al [18] for men diagnosed in the pre-PSA era (Table 3). The long-term decline in mortality rates is probably because of the greater survival of men with relatively indolent tumors.

Critics of the SPCG-4 and PIVOT trials [6, 19] often question whether these trials apply to contemporary men in the USA diagnosed with cancer following PSA testing. Our findings that 15-yr PCSM rates for a cohort of US men diagnosed in the PSA era are comparable to or better than those in the observation arms of these studies suggest that older men with PSA-detected low-grade cancers have a very modest risk of disease progression. Our results also confirm the findings of smaller subgroup analyses that radical prostatectomy is not associated with improved disease-specific survival or overall survival for men aged ≥65 yr with low-risk disease [6].

We also examined changes in PCSM rates following diagnosis. Mortality rates were relatively stable from 6 to 15 yr following diagnosis. This finding is similar to that reported by Albertsen et al [17] but differs from that reported by Johansson et al [18], who observed continued increases beyond 15 yr of follow-up. Men diagnosed with localized prostate

cancer have a range of pathologic findings. Men with relatively indolent tumors are likely to survive for 15–20 yr. Men with more aggressive tumors usually succumb to their disease within 15 yr of diagnosis. We believe that this is the reason for the lower mortality rates observed after 15 yr. Given that screening was relatively rare for the Johansson cohort, we believe that our study results are more likely to resemble the experience of contemporary patients. The substantial improvement in outcomes observed in our study when compared to earlier work by Albertsen et al [17] and Johansson et al [18] could be attributable to several factors, including diagnosis lead time, Gleason score migration, and length-time bias arising from screening detection [20, 21]. PSA testing can identify disease 6–13 yr before it presents clinically, resulting in a large lead-time and a longer survival period [22]. Gleason score migration, whereby formerly lower-grade disease is now classified in a higher-grade category, introduces a Will Rogers effect that produces an artifact of improved survival [23]. PSA testing may also introduce a length-time selection bias by identifying indolent cancers, which may be associated with better survival.

Despite the large sample size and timeliness of the data, our study has some limitations. Our data may be subject to selection bias. Men in our study cohort did not receive surgery or radiation and may have had much more favorable disease (but greater competing risks of death from other causes) compared to men receiving treatment. Nevertheless, the results largely parallel those observed in the PIVOT and SPCG-4 trials, which included a clinical trial population selected for lower competing risks of death from other causes, but less favorable disease. The similarity in results suggests that the balance between competing risks of death from other causes and disease aggressiveness might be similar in the two populations.

Our study results may not apply to younger men because our analysis was restricted to men aged ≥ 65 yr. Results from the SPCG-4 trial suggest that younger men may benefit from radical prostatectomy [4, 5]. In addition, because of limitations of the SEER registry database, our study is unable to differentiate Gleason 4 + 3 from Gleason 3 + 4, as well as grouping Gleason 7 with those < 7 . Men with Gleason 7 tumors may face a greater threat of disease progression, and therefore may benefit from surgery, as suggested by the SPCG-4 study. In the study by Albertsen et al [21], men with Gleason 7 cancers had a substantially greater risk of dying from their disease compared to men with Gleason 5–6 disease. Therefore, our competing-risks analysis may overestimate PCSM rates for men with Gleason 5–6 disease and underestimate rates for men with Gleason 7 disease. Similar considerations may apply for Gleason 3 + 4 compared to Gleason 4 + 3 disease.

Since the Medicare database does not consistently capture the use of oral agents such as antiandrogens, our analysis may have missed some secondary cancer therapies. However, data from the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) database [24] show that antiandrogens are only used as the sole treatment for localized prostate cancer in approximately 2% of men, suggesting a minimal impact at best. Our study has important strengths. The study was population-based and all-inclusive in the regions studied, rather than limited to specific institutions or networks. Consequently, the results are likely to apply more broadly. In addition, the study included substantially more data than

previous reports. Finally, the study provides information on over 10 000 men aged 75 yr, a group of patients often omitted from clinical trials.

5. Conclusions

In summary, our findings show that 15-yr outcomes following conservative management of contemporary PSA era patients aged 65 yr with localized prostate cancer are substantially more favorable than previously reported. Specifically, the outcomes are similar or superior to those for men in the control arms of the PIVOT trial [6] and SPCG-4 trial [4, 5]. Elderly men with low-grade disease are unlikely to benefit from radical prostatectomy and should consider active surveillance or conservative management as the preferred initial treatment option. Men with high-grade disease face a more significant threat of mortality from cancer and may want to consider more aggressive treatment. Finally, our data suggest that PCSM rates stabilize over time, resulting in a limited propensity to increase over longer follow-up.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Disclaimer: This study utilizes the linked SEER-Medicare database. The interpretation and reporting of these data are the sole responsibility of the authors. The content of the information does not necessarily reflect the position or the policy of the Government, and no official endorsement should be inferred.

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Take Home Message

The rate of 15-yr prostate cancer mortality was low among patients with prostate-specific antigen-detected Gleason 5–7 disease initially treated with conservative management. This suggests that conservative management is a reasonable option for older men with newly diagnosed low-grade prostate cancer.

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Fig. 1. Competing risks of death by age at diagnosis, cancer stage, and grade. Dark shading indicates prostate cancer-specific mortality and light shading mortality due to competing causes; nonshaded areas represent the probability of being alive. Results for well-differentiated disease are not shown because estimates were unstable due to limited sample sizes.

Table 1

Characteristics of 31 137 men receiving conservative management for clinically localized (T1 or T2) prostate cancer

Parameter	Result
Age at diagnosis (yr)	75 (72–82)
Follow-up (mo)	105 (65–150)
Black race	4,262 (14)
Married at diagnosis	17,995 (58)
Urban residence	26,093 (84)
Zip code–level income (US\$)	\$44 545 (\$33 908–\$58 880)
SEER regions	
Northeast	5316 (17)
North-central	5422 (17)
West	15 315 (49)
South	5084 (16)
Gleason score	
2–4	3223 (10)
5–7	23 934 (77)
8–10	3980 (13)
Clinical stage ^a	
T1c	11 755 (40)
T2	17 978 (60)
Charlson comorbidity score ^b	
0	22 393 (72)
1	5214 (17)
2	3124 (10)
Unknown	406 (1.3)
Year of diagnosis	
1992–1997	7846 (25)
1998–2003	10 401 (33)
2004–2009	12 890 (41)
Alive at last follow-up as of December 31, 2009	20 508 (61)

Data are presented as median (interquartile range) for continuous variables and *n* (%) for categorical variables.

^aSEER clinical extension information was used to determine cancer stage (T1, T2).

^bCharlson comorbidity score was derived from Medicare claims during the year before prostate cancer diagnosis using a validated algorithm [25].

15-yr competing risks of prostate cancer specific mortality and overall mortality among men with initial conservative management ^a

Table 2

Treatment	65–74 yr at diagnosis						75 yr at diagnosis					
	PSA-detected T1c			Non-PSA-detected			PSA-detected T1c			Non-PSA-detected		
	Events (n)	15-yr risk (95% CI)		Events (n)	15-yr risk (95% CI)		Events (n)	15-yr risk (95% CI)		Events (n)	15-yr risk (95% CI)	
Gleason 5–7												
Overall	968	49.2 (44.9–55.4)		2035	59.3 (56.6–62.1)		2065	86.5 (82.5–93.2)		5025	90.2 (88.5–91.5)	
Prostate	65	5.7 (3.7–8.0)		259	10.8 (9.2–12.8)		186	10.1 (8.1–12.4)		568	13.6 (12.2–15.2)	
Gleason 8–10												
Overall	178	81.2 (64.6–93.6)		589	82.3 (76.7–86.5)		459	92.1 (86.3–98.0)		1,608	96.7 (95.2–98.2)	
Prostate	51	22.4 (15.7–34.5)		200	29.0 (24.3–33.7)		105	27.1 (20.6–32.6)		415	26.0 (23.1–28.8)	

^aProstate cancer mostly based on SEER data as of December 31, 2009. Overall mortality based on vital status as of December 31, 2011.

Table 3

Unadjusted prostate cancer mortality rates by follow-up period

Follow-up	Mortality rate per 1000 (95% confidence interval)		
	Our study ^a (diagnosed 1992–2009)	Albertsen et al [17] (diagnosed 1971–1984)	Johansson et al [18] (diagnosed 1977–1984)
0–5 yr	10 (9–11)	30 (24–36)	12 (7–22)
6–10 yr	19 (18–21)	33 (25–42)	18 (10–33)
11–15 yr	23 (20–27)	40 (28–52)	15 (6–26)
>15 yr	22 (12–41)	17 (8–29)	44 (22–88)

^a Our data exclude patients with Gleason 2–4 disease.

15-yr cumulative risk of selected secondary cancer treatments after diagnosis in patients with localized prostate cancer with initial conservative management

Table 4

Treatment	65–74 yr at diagnosis			75 yr at diagnosis		
	PSA-detected T1c			PSA-detected T1c		
	Events (n)	15-yr risk (95% CI) ^a	Events (n)	15-yr risk (95% CI) ^a	Events (n)	15-yr risk (95% CI) ^a
Gleason 5–7						
Any therapy ^a	2401	53.6 (51.6–56.3)	2616	51.0 (49.5–52.8)	1590	44.6 (42.1–47.4)
ACT	2055	45.5 (42.8–48.5)	1914	35.3 (34.1–37.0)	685	16.9 (15.5–18.1)
ADT	736	23.6 (20.6–26.7)	1217	27.6 (25.7–29.3)	1131	33.4 (31.4–35.7)
Chemotherapy	96	4.9 (3.4–7.2)	149	4.8 (3.8–5.9)	109	3.7 (2.8–4.9)
Palliative radiation ^b	94	3.2 (2.6–4.1)	151	4.0 (3.3–4.7)	79	2.6 (2.0–3.3)
Gleason 8–10						
Any therapy ^a	191	53.6 (47.9–63.6)	480	53.2 (50.1–57.6)	260	49.3 (40.7–54.3)
ACT	120	34.8 (30.2–48.1)	239	26.1 (23.8–30.5)	66	12.3 (8.9–14.7)
ADT	126	38.0 (31.5–44.0)	361	42.7 (38.8–47.1)	238	45.1 (37.2–49.6)
Chemotherapy	25	8.3 (5.2–11.8)	64	9.2 (6.2–12.3)	24	5.4 (3.1–8.0)
Palliative radiation ^b	19	7.4 (4.5–11.0)	68	8.2 (6.2–10.3)	23	4.5 (2.8–6.4)

ACT = attempted curative therapy; ADT = androgen deprivation therapy.

^aCumulative risks were derived from a competing-risks model with death as the competing risk.

^bFewer than 20 visits for radiation therapy during a 6-wk period.

^cConfidence intervals were estimated using bootstrapping with 1000 replications.